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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/508,957
Filing Date: February 03, 2005
Appellant(s): STAMLER ET AL.

Eric S. Spector
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed December 5, 2008 appealing from the Office action mailed July 9, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

Withdrawn Rejections

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. Rejection of Claims 75-83 are under 35 U.S.C. 112, second paragraph in regards to "administering inactivated mtALDH activating effective amount of agent" is withdrawn. Rejection of Claim 84 is rejected under 35 U.S.C. 112, second paragraph in regards to "a nitroglycerin sensitivity restoring amount" is withdrawn.

New Ground of Rejection

Claim 84 is rejected under 35 U.S.C. 102(b) as being anticipated by Weischer et al.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

DE 4420102 A1 WEISCHER et al. 12-1995

Weischer et al., machine translation from EPO of DE4420102-description, 1995-generated and printed 7/11/2007, 11 pages

Weischer et al., machine translation from EPO of DE4420102-claims, 1995-generated and printed 7/11/2007, 2 pages

Pruijn et al. "Interplay between Vitamin E, Glutathione and Dihydrolipoic Acid in Protection against Lipid Peroxidation", Vol. 93, Issue 6 (1991), Abstract only (pages 1-2)

Getz et al. "A Comparison between the Sulfhydryl Reductants Tris (2-carboxyethyl) phosphine and Dithiothreitol for Use in Protein Biochemistry", Analytical Biochemistry, Vol., 273 (1999), pages 73-80

Physicians Desk Reference Electronic Library, "NITRO-DUR", Rev. 12/04, copyright 1987, 2002, http://www.thomsonhc.com/pdrel/librarian, pages 1-8

Physicians Desk Reference Electronic Library, "NITROLINGUAL PUMPSPRAY", Rev. 6/06, http://www.thomsonhc.com/pdrel/librarian, pages 1-8

Kennedy et al., "Airway Response to Sublingual Nitroglycerin in Acute Asthma", July 10, 1981, JAMA, Vol. 246, No. 2, pages 145-147

Physicians' Desk Reference, "NITRO-BID - CAPS and IV", 1989, Ed.43, Pages 1220-1221.

(9) Grounds of Rejection

The following grounds of rejection are applicable to the appealed claims:

(A) Claims 75-84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. (New Matter)

The claims are drawn to administering dihydrolipoic acid, dithiothreitol, or tris (2-carboxyethylphosphine) to a patient no longer responsive to nitroglycerin. The disclosure teaches the administration of these compounds for patients with nitroglycerin tolerance generically but does not specifically recite and target a patient which is completely tolerant. Nitrate tolerance is a loss of clinical sensitivity which is very broad and can be mild, moderate, severe, and many other degrees. Loss of clinical sensitivity is not, however, the same as complete tolerance in which a patient is not responsive at all. There is also no support in the specification for the term "nitroglycerin sensitivity restoring amount" of dihydrolipoic acid, dithiothreitol, or tris (2-carboxyethylphosphine).

(B) Claims 75-84 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of angina, an unstable coronary syndrome, it does not reasonably provide enablement for conditions more generally.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In*

re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). Those factors are addressed as follows:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a patient that is completely tolerant to nitroglycerin, with no specific condition being recited. Additionally, the claims recite a "nitroglycerin sensitivity restoring amount" of dihydrolipoic acid, dithiothreitol, or tris (2-carboxyethylphosphine).

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the prior art shows that nitroglycerin is currently advised for use in angina but the benefits for conditions such as congestive heart failure have not been established to date, and are contraindicated in acute myocardial infarction, constrictive pericarditis, and pericardial tamponade (see previous Physician Desk Reference pages). As taught by Kennedy et al. (Airway response to sublingual nitroglycerin in acute asthma, JAMA), nitroglycerin was inadequate for the treatment of acute asthma and did not significantly change neither the forced expiratory volume nor the forced vital capacity of air for those tested showing that nitroglycerines in not adequate initial therapy for asthmatic attacks, in fact he teaches that its use could be dangerous. Applicant submitted two journal abstracts: Rolla, G., et al., Pulmonary Pharmacology

1995, April - June, 8(2-3): 137-141 and Sharara, A.M., et al., Pulmonary Pharmacology and Therapeutics 11(1), 65-70 (February 1998), stating others found a benefit of nitroglycerin for asthma. The abstract by Rolla et al. is teaching the effect of nitroglycerin pretreatment for the effectiveness of the beta-agonists (e.g. salbutamol) and theophylline administered which are the treating agents in the abstract, not the nitroglycerin. The abstract by Sharara, A.M., et al. states that there is conflicting reports regarding the efficacy of GTN as a bronchodilator (second sentence of abstract). The study was on 18 patients and while bronchodilating effects were seen, the mechanism is not known; there is no indication as to why the results are different from those in Kennedy et al., especially as Sharara states that there are conflicting reports on the issue. This underscores the unpredictability of the drug for enablement for asthma and that there is no reasonable expectation for success to the degree that it is not currently recommended for treatment asthma (see previous PDR pages from 2006). The unpredictability for the drug in the art is high and it is unclear what conditions nitroglycerin would be effective, much less what the outcomes would be when combined with another drug, resulting in an unclear expectation of what would be successful, including how other drugs affect the tolerance or their potential to block nitroglycerin to affect tolerance.

(5) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance solely for the treatment of angina with nitroglycerin in Examples XXXII and XXXIII. However, the specification does not provide for all possible conditions for nitroglycerin treatment and tolerance.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the high degree of unpredictability in the art for nitroglycerin, it is unclear under what conditions nitroglycerin would be effective, much less what the outcomes would be when combined with another drug. Practicing the invention would require undue experimentation of one skilled in the art to address each and every condition and every combination without a clear expectation of success.

Claim Rejections - 35 USC § 102

(C) Claims 75-78 and 81 are rejected under 35 U.S.C. 102(b) as being anticipated by Weischer et al. (DE 4420 102 A1).

Weischer et al. teaches the use of alpha-lipoic acid, also known as dihydrolipoic acid, in combination with cardiovascular drugs, including specific embodiments for nitroglycerin (glyceryl trinitrate), for several conditions including angina and nitrate tolerance.

It is noted that the translation provided is a machine translation from the European Patent Office and for clarity "alpha Liposaure" is alpha-lipoic acid and "Glyceroltrinitrate" is nitroglycerin.

Weischer teaches the combination of alpha-lipoic acid (enantiomers, derivatives or metabolites) and organic nitrates, including nitroglycerin in combination preparation. He teaches that the combination showed a greater anti-ischemic effect than when the nitroglycerin was administered alone. Thereby the combination of nitroglycerin and other nitrates with alpha-lipoic acid/dihydrolipoic acid (dithiol) showed a therapeutic anti-organic nitrate tolerance effect (a reduction of a loss of sensitivity). There were in vitro and in vivo models performed.

The patients will inherently have some degree of tolerance as administration of nitroglycerin produces tolerance that increases over time and angina is a chronic condition (see DE 4420102, Page 6, Table 1). Administration of the combination to angina patients will inherently affect tolerance as the limiting step is administration of alpha-lipoic acid/dihydrolipoic acid (dithiol). The process of affecting the tolerance would inherently occur once administered to the patient.

Weischer goes on to claim the method of use in Claim 21 of nitroglycerin and other nitrates with alpha-lipoic acid/dihydrolipoic acid (dithiol) for angina pectoris, nitrate

tolerance, among other conditions (citations are based on the translation provided – Specification: Page 1, paragraphs 1, 7, 9, 16-17 of 19 on page, Page 2, paragraphs 2-9 of 18 on page, Page 4, paragraph 2-10 of 28 on page, Page 6, paragraph 10-14 of 21 on page, Page 7, paragraph 14 of23 on page, Claim set: Page 2, claim 21).

All the critical elements are taught by the cited reference and thus the claims are anticipated.

Claim Rejections - 35 USC § 103

(D) Claims 75-77, 79, and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weischer et al. (DE 4420 102 A1) in view of Pruijn et al. (Interplay between Vitamin E, Glutathione and Dihydrolipoic Acid in Protection against Lipid Peroxidation).

The teachings of Weischer et al. are addressed above.

Weischer et al. does not expressly teach the use dithiothreitol (DTT).

Pruijn et al. teaches that dihydrolipoic acid is an effective thiol, especially as a reducing agent. It was tested along with dithiothreitol (DTT) and glutathione in the presence of thiol-alkylating agents. DTT and dihydrolipoic acid were able to reverse the inhibition of the alkylating agents with DTT reversing the inhibitory effects of all three alkylating agents and the dihydrolipoic acid reversing only one alkylating agent (ebselen). Glutathione however was not able to reverse the inhibitory effects.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize dithiothreitol (DTT), as suggested by Pruijn, and produce the instant invention.

As DTT was able to reverse the inhibitory effects of all three alkylating agents and the dihydrolipoic acid was able to reverse only one alkylating agent (ebselen), it would have been obvious to one of skill in the art at the time of the invention to substitute DTT for dihydrolipoic acid as the effective reductant for the same capacity to combine with the nitroglycerin. Pruijn taught that dihydrolipoic acid and DTT are effective thiols, especially as reducing agents. One of skill in the art at the time would utilize DTT as it has many reductant and protective properties, especially its in light of its ability to overcome inhibition in comparison to glutathione and dihydrolipoic acid.

One of ordinary skill in the art would have been motivated to do this because utilization of a more effective reductant such as would result in a more effective therapy and product which is always desirable.

(E) Claims 75-83 are rejected under 35 U.S.C. 103(a) as being unpatentable Weischer et al. (DE 4420 102 A1) in view of Pruijn et al. (Interplay between Vitamin E, Glutathione and Dihydrolipoic Acid in Protection against Lipid Peroxidation), and in view of Getz et al. (A Comparison between the Sulfhydryl Reductants Tris(2-carboxyethyl)phosphine and Dithiothreitol for Use in Protein Biochemistry, Analytical Biochemistry).

The teachings of Weischer et al. (DE 4420 102 A1) in view of Pruijn et al. are discussed above.

Weischer et al. (DE 4420 102 A1) in view of Pruijn et al. does not expressly teach the use of tris(2-carboxyethyl)phosphine.

Getz et al. teaches that the sulfydryl reductant tris(2-carboxyethyl)phosphine (TCEP) is an attractive alternative to commonly used dithiothreitol (DTT). The reductants preserve enzymatic activity that is sensitive to sulfhydryl oxidation equally. However, TCEP is desirable because it is more stable than DTT especially for long-term storage wherein DTT would require metal chelates in the buffer for preservation.

TCEP is noncompetitive with protein sulfydryls for attachment of thiol-reactive dyes giving TCEP a major advantage over DTT. Getz concluded that TCEP had clear advantages over DTT, and thereby preferable, but the choice of reductant is application specific (Abstract, Page 73, 2nd column, Page 74, 1st column, Page 80).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute tris(2-carboxyethyl)phosphine for DTT, as suggested by Getz, and produce the instant invention. One of skill in the art at the time would utilize tris(2-carboxyethyl)phosphine as it has many advantages over DTT, especially its stability for testing, administration, and manufacture.

One of ordinary skill in the art would have been motivated to do this because tris(2-carboxyethyl)phosphine is especially stable over DTT, particularly with out the presence of a metal chelates. Stability is critical for any drug for storage, administration, and manufacture. The fact that an additional ingredient is not required for stability

reduces costs, increases storage time, and the duration of use of the drug to be administered.

(F) Claim 84 is rejected under 35 U.S.C. 102(b) as being anticipated by Weischer et al. (DE 4420 102 A1). (New Ground of Rejection)

Claim 84 had been inadvertently omitted during prosecution. This new ground of rejection corrects that oversight.

Weischer et al. teaches the use of alpha-lipoic acid, also known as dihydrolipoic acid, in combination with cardiovascular drugs, including specific embodiments for nitroglycerin (glyceryl trinitrate), for several conditions including angina and nitrate tolerance.

(10) Response to Argument

(A) Written Description, Claims 75-84.

Appellant argues that the invention need not be described explicitly in the specification to provide for a patient that no longer responds to nitroglycerin and if a skilled artisan would understood the inventor to be in possession of the claimed invention at the time of filing then every nuance of the claims not explicitly described would have adequate description. The examiner respectfully disagrees with this assertion as the specification must address and describe what the method is and what patient population is being treated with the methods.

Appellant also argues that claim 75 is directed to treating a nitroglycerin patient with agents that activate inactivated mtALDH and the patient is treated without reference to the disorder for which nitroglycerin was needed to cause tolerance. Appellant cites several areas of the specification asserting that these areas support written description.

Page 1, line 1-5 is cited as support for the invention to be directed to therapies for patients for nitroglycerin therapy, and citing Page 3 line 15-20 as an area to support that nitroglycerin tolerance can be reversed and this is supportive of contemplating administering the compounds to a patient that is no longer responsive to nitroglycerin to reverse the tolerance. The examiner respectfully disagrees with this assertion as Applicant's reference to the lines of Page 1 of the specification does not support the patient population addressed in the claims. The claims are to for administration to patients who are no longer responsive to nitroglycerin. This is different than tolerance to nitroglycerin which is the decrease of sensitivity of nitroglycerin in a patient over time where you have to gradually increase the amount of nitroglycerin to get the desired level of clinical response to nitroglycerin over time. This does not mean that there is no response to the nitroglycerin being delivered. This means that the amount given did not result in the level of response desired, so more nitroglycerin is delivered to get the desired level of response as addressed in Page 1 last paragraph-Page 2 line 2 of the specification. A patient can also have a response to nitroglycerin that is subclinical, meaning that there is no apparent clinical effect but that is not equivalent to not having a response to the drug.

The recitation that the patient is "no longer responsive to nitroglycerin" which means that the patient is completely tolerant whereby there is no response, no enzyme activity/response, no effect, nor sensitivity whatsoever. A patient which is sensitive/responsive to the nitroglycerin but is subclinical (has no clinical showing) is not a patient who is "no longer responsive to nitroglycerin". It is noted that the phrase encompasses a patient who is completely tolerant with no enzymatic response currently and in the future, which leaves the population inconsistent as someone who is completely tolerant (no sensitivity, no enzyme response, no response whatsoever) to a drug today may not be completely tolerant to the same drug years from now.

Appellant cites page 1, line 1-5 of the specification as and area of support which is the cross-reference to related applications and benefit claims. If Appellant meant Page 1 line 5-10 of the specification as an area of support, the section is directed to therapy for patients for whom nitroglycerin administration is indicated, screens for the appropriateness of nitroglycerin treatment, cross-tolerance, dose determination, and a nitroglycerin composition for intravenous administration. This area of the specification however, does not support the claimed subject matter as it is not to the administration of dihydrolipoic acid (DHLA), dithiothreitol (DTT), or TCEP (tris(2-carboxyethylphosphine)) for the activating the inactive mtALDH to the specific patient population of patients who received nitroglycerin therapy and are now "no longer responsive to nitroglycerin". This area of the specification is directed to screening processes, dose determination, and therapy for patient who need nitroglycerin (nitroglycerin administration is indicated) but there is no specific support for a patient who is completely tolerant to the nitroglycerin

which actually would be viewed as a patient where nitroglycerin would not be indicated. Page 3 line 15-20 goes to intravenous administration of a composition of GTN (nitroglycerin) where the tolerance is reversed but is not commensurate in scope with the claims as the support is for intravenous administration which is not recited in the claims and the patient population of the claims ("no longer responsive to nitroglycerin") is not the general population of nitroglycerin tolerance as recited in the this area of the specification for the same reasons as addressed above.

Appellant cites Page 11, line 20 to Page 12 line 20 of the specification as having the phrase "capable of activating mtALDH" for compounds and dosages for those in claim 75. Appellant cites Background 4 as an area reciting dosages for the compounds of claim 75 and Figure 1. Appellant asserts that these areas provide dosages for DTT, DHLA, and TCEP and support that the specification discusses reversing nitroglycerin tolerance or restoring nitroglycerin sensitivity in a patient that no longer responds to nitroglycerin and one skilled in the art would consider these teachings supportive of the written description requirement. The examiner respectfully disagrees with this assertion as the area of the specification on Pages 11-12 is to general definitions and the dosages recited are to the amount of nitroglycerin not to DTT, DHLA, or TCEP to be administered for different medical conditions. The Background Example 4 and Figure 1 are directed to the amounts of the compounds (e.g. DTT, DHLA, TCEP) in macrophage (in vitro) testing which is was to determine efficacy between the compounds but are not amounts for administration to a patient. There is also no support for one who is "no

longer responsive to nitroglycerin" which is distinct from a patient who is nitroglycerin tolerant as addressed above.

Appellant also cites Examples XXXII and XXXIII on page 45 as supportive and a showing of restoring sensitivity of nitroglycerin in a patient. Appellant also asserts that the examples while directed to angina are viewed by Examiner in the Final Rejection as insufficient as they are to merely angina. The examiner respectfully disagrees with this assertion as the Final Rejection addresses the treatment in the examples toward the issue of enablement which is addressed below, not written description . The patients in the examples do not support Appellant's assertion for support for the patient population of the claims, since the examples are to patients who are nitroglycerin tolerant which as addressed above, is known in the art and described in the specification to the decrease of clinical effectiveness of a drug (e.g. nitroglycerin) over time where increased dosages are needed over time to result in the desired level of clinical response. The patients in Example XXXII and XXXIII are tolerant but does not address what degree of tolerance, the patients can be tolerant and still receive the desired response if the dosage is increased, the patient be nominally responsive, subclinically responsive (has a response that is not clinically apparent or effective), or have a enzymatic response which is not a patient that is no longer responsive to nitroglycerin, wherein the patient has no response-clinical, subclinical, or enzymatic whatsoever. This is a distinction known in the art. There is no indication, testing, or teaching showing that the patients are completely tolerant wherein the patient is no longer responsive to nitroglycerin to provide support for the claimed subject matter. Appellant's assertion that there is no

indication that one skill in the art would not consider the additional teachings of the specification when reviewing the examples and as a result, the claims as a whole would be recognized by one of skill in the art as being in the possession of the Appellant.

The examiner respectfully disagrees with this assertion as there is no indication that one of skill in the art would view these areas of the disclosure as to the method of addressing nitroglycerin tolerance beyond the general view of the term which is also addressed in the specification as the range of tolerance where one is treated by increasing the dosage of the nitrate to attain the desired clinical result. The term can also be viewed to encompass a patient where the patient may no longer express a *clinical* response upon administration of the nitroglycerin but that is not the same nor would be viewed as the neither same nor supportive as a patient who is no longer responsive to nitroglycerin. A patient who is no longer responsive to nitroglycerin is one that does not have any response to nitroglycerin. There is no clinical response, there is no subclinical response, there is no enzymatic response, and there is *complete* tolerance. The patient population being addressed is additionally variable as one who may be completely tolerant today may not necessarily be completely tolerant years from now wherein would the patient meet the recitation as it cites as completely tolerant with no variance. The issues in regards to the cited areas of the specification are addressed above. There is no support in the disclosure for the method for the patient population cited in the claims.

Appellant asserts that claim 84 is supported for the patient who is "no longer responsive to nitroglycerin" is supported for the same reasons as claim 75. The

examiner respectfully disagrees with this assertion as addressed above for claim 75. Appellant asserts that the phrase "nitroglycerin sensitivity restoring amount" is supported by Page 11 line 20-Page 12 line 20, Background Example 4, and Figure 1 supplies dosages. Appellant also asserts that Examples XXXII and XXXIII on page 45 show restoring sensitivity to nitroglycerin in a patient. The examiner respectfully disagrees with this assertion because Page 11 line 20-Page 12 line 20 as addressed above, is to general definitions and the dosages recited are to the amount of nitroglycerin not to DTT, DHLA, or TCEP to be administered for different medical conditions. The Background Example 4 and Figure 1 are directed to the amounts of the compounds (e.g. DTT, DHLA, TCEP) in macrophage (in vitro) testing which is was to determine efficacy between the compounds but are not amounts for administration to a patient. As for Examples XXXII and XXXIII, as addressed above the amount of dihydrolipoic acid and TCEP used in the examples are for addressing nitrate tolerance not and amount for one who is "no longer responsive to nitroglycerin" which is distinct from a patient who is nitroglycerin tolerant as addressed above. The claimed subject matter is thereby not supported by the disclosure and are rejected is being to new matter.

(B) Scope of enablement, Claims 75-84

Appellant argues that the claims are independent of the disease for which nitroglycerin is administered and directed to restoring clinical sensitivity of nitroglycerin

to a patient who has lost clinical sensitivity to nitroglycerin and as a result, a condition that would not be treated with nitroglycerin would not be encompassed by the claims. Appellant also addresses the rejection as conjecture and that the art provided shows the state of the art and one of skill in the art would know what condition could be treated by nitroglycerin. The examiner respectfully disagrees with this assertion as the claims are first directed to affecting nitroglycerin tolerance with the administration of DTT, DHLA, or TCEP to a patient who is no longer responsive to nitroglycerin which is not the same scope as one who has lost clinical sensitivity. Second, Appellant's assertion that the claims are independent of the disease and a condition not treated with nitroglycerin would not be encompassed but the claims include angina, restenosis, heart failure, portal hypertension, asthma, and rectal spasm where several of these conditions are not indicated for use with nitroglycerin. As the claims appeared to encompass any condition as several of the claimed conditions are not indicated for administration of nitroglycerin and are in some cases contraindicated the claims were treated to encompass any condition. Third in regards to the art presented, it is no only reflective of the art but also reflective to what conditions are treated with nitroglycerin and several of the claimed conditions are not treated with nitroglycerin. An example is asthma (claimed) which is taught to be inadequate for acute asthma by Kennedy et al., and as indicated by the PDR, acute myocardial infarction, constrictive pericarditis, and pericardial tamponade are all forms of heart failure (claimed) and are contraindicated for use with nitroglycerin. The PDR states that the known indicated use for nitroglycerin is for angina which is also exemplified in the specification. There is no other condition

indication in the PDR for nitroglycerin, which is not conjecture but evidence supported by art from a standard in the industry, and as a result the claims are subject to the scope of enablement as the claims appeared to encompass any condition as several of the claimed conditions are not indicated for administration of nitroglycerin and are in some cases contraindicated.

In regards to Appellant's assertion that Page 11 line 20-Page 12 line 20 provides dosages for the compound in the claims, Background Example 4 for dosages for the compounds, and Example XXXII and XXXIII for dosages, the examiner respectfully disagrees with these assertions. As addressed in the rejections above, Page 11 line 20-Page 12 line 20 as addressed above, is to general definitions and the dosages recited are to the amount of nitroglycerin not to DTT, DHLA, or TCEP to be administered. The Background Example 4 is directed to the amounts of the compounds (e.g. DTT, DHLA, TCEP) in macrophage (in vitro) testing which is was to determine efficacy between the compounds but are not amounts for administration to a patient. As for Examples XXXII and XXXIII, as addressed above the amount of dihydrolipoic acid and TCEP used in the examples are for angina which is the condition not subject to enablement. However, there is no guidance for the remaining conditions encompassed by the claims and as the art states that several claimed conditions are contraindicated and the only indicated condition for nitroglycerin in the PDR is angina, the claims are subject to the scope of rejection.

It is noted that Appellant's personal opinions in regards to 112 rejections is not an argument relevant to the merits of the rejections presented and the grounds and assertion have been addressed above.

(C) Anticipation, Claims 75-78 and 81

Appellant asserts that while Weischer et al. teaches the combination of alpha-lipoic acid (known as dihydrolipoic acid or DHLA) for nitroglycerin tolerance, Weischer never administers the combination for a patient no longer responsive to nitroglycerin. Appellant asserts that Weischer is direct to prevent nitrate tolerance not addressing a patient who is no longer responsive to nitroglycerin. Appellant asserts that Weischer potentiates a response and that does not mean restoration referencing articles to N-acetylcysteine. Appellant also asserts that the mechanism for the biotransformation of nitroglycerin with mtALDH is not addressed by Weischer and was discovered by Appellant.

The examiner respectfully disagrees with these assertions as first, if the term tolerance is to be viewed as asserted by Appellant to support the patient population the is no longer responsive to nitroglycerin, then alternatively the art of Weischer would also have be viewed to encompass patients who are no longer responsive to nitroglycerin when addressing tolerance. Tolerance is also developed as known in the art and addressed in the instant specification on Page 1 last paragraph -Page 2 line 2 as nitroglycerin is delivered. Once a patient starts nitroglycerin treatment, tolerance begins

and increases over time. Appellant's assertion that it is directed to prevention is not consistent with the reference as Weischer teaches the use of DHLA with nitrates including nitroglycerin (glyceryl trinitrate) for several conditions including the *treatment of angina and organic nitrate tolerance* (Page 1-2 of the machine translation, claims 1-3 and 21, and Page 4 -Table 1). The assertion that Weischer is addressing a potentiation not reversal is not reflective of the reference as it is administration with the claimed compound DHLA and .nitroglycerin (glyceryl trinitrate) for treatment of the conditions addressed including angina and organic nitrate tolerance. The assertion of N-acetylcysteine is not relevant to the art of Weischer. As for the assertion that there is no teaching for the mechanism for mtALDH, the Examiner respectfully disagrees as Weischer teaches the administration with the claimed compound DHLA and .nitroglycerin (glyceryl trinitrate) for treatment of the same conditions including angina and organic nitrate tolerance. The resulting mechanism for the resulting treatment is inherent upon the administration of the agents DHLA and nitroglycerin. While the discovery of an unappreciated property of the prior art or a scientific explanation for the prior art functioning, is a scientific advancement as an explanation, it does not render the claims patentable as the mechanism is inherent in the prior art presented.

(D) Obviousness, Claims 75-77, 79, and 82

As addressed above, if the term "tolerance" in the disclosure is viewed to support the patient population of one who "no longer is responds to nitroglycerin" then alternatively the following art rejections would apply.

Appellant's assertions in regards to Weischer are addressed above including the issue of tolerance.

Appellant's assertion in regards to Pruijn is that Pruijn does not disclose or suggest the mtALDH mechanism or it administration with nitroglycerin for affecting nitroglycerin tolerance.

The examiner respectfully disagrees with these assertions as the assertions are against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

Weischer et al. taught the use of the DHLA with nitroglycerin for the treatment of angina and nitrate tolerance. Pruijn et al. taught that dihydrolipoic acid is an effective dithiol, especially as a reducing agent and DTT and dihydrolipoic acid were able to reverse the inhibition of the alkylating agents with DTT reversing the inhibitory effects of all three alkylating agents and the dihydrolipoic acid reversing only one alkylating agent (ebselen). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize a more effect dithiol such as dithiothreitol (DTT), as DTT was able to reverse the inhibitory effects of all three alkylating agents and the dihydrolipoic acid was able to reverse only one alkylating agent (ebselen). One of ordinary skill in the art would have been motivated to do this because utilization of a

more effective reductant such as would result in a more effective therapy and product which is always desirable.

(E) Obviousness, Claims 75-83

As addressed above, if the term "tolerance" in the disclosure is viewed to support the patient population of one who "no longer is responds to nitroglycerin" then alternatively the following art rejections would apply.

Appellant's assertions in regards to Weischer et al. are addressed above including the issue of tolerance.

Appellant's assertions in regards to Pruijn et al. are addressed above.

Appellant's assertions in regards to Getz are that the reference does not disclose or suggest the mtALDH mechanism or it administration with nitroglycerin for affecting nitroglycerin tolerance.

The examiner respectfully disagrees with these assertions as the assertions are against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

Weischer et al. taught the use of the DHLA with nitroglycerin for the treatment of angina and nitrate tolerance. Pruijn et al. taught that dihydrolipoic acid and DTT are effective reducing agents and were able to reverse the inhibition of the alkylating agents. Getz et al. teaches that the sulfydryl reductant tris(2-carboxyethyl)phosphine (TCEP) is an attractive alternative to commonly used dithiothreitol (DTT) because while

both reductants preserve enzymatic activity that is sensitive to sulfhydryl oxidation equally, TCEP is desirable because it is more stable than DTT especially for long-term storage wherein DTT would require metal chelates in the buffer for preservation.

(F) Anticipation, Claim 84 (New Ground of Rejeciton)

Appellant assertions in regards to Weischer et al. are addressed above, and the Examiner's statements for the application of Weischer are also addressed above.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

This examiner's answer contains a new ground of rejection set forth in section **(9)** above. Accordingly, appellant must within **TWO MONTHS** from the date of this answer exercise one of the following two options to avoid *sua sponte* **dismissal of the appeal** as to the claims subject to the new ground of rejection:

(1) **Reopen prosecution.** Request that prosecution be reopened before the primary examiner by filing a reply under 37 CFR 1.111 with or without amendment, affidavit or other evidence. Any amendment, affidavit or other evidence must be relevant to the new grounds of rejection. A request that complies with 37 CFR

41.39(b)(1) will be entered and considered. Any request that prosecution be reopened will be treated as a request to withdraw the appeal.

(2) **Maintain appeal.** Request that the appeal be maintained by filing a reply brief as set forth in 37 CFR 41.41. Such a reply brief must address each new ground of rejection as set forth in 37 CFR 41.37(c)(1)(vii) and should be in compliance with the other requirements of 37 CFR 41.37(c). If a reply brief filed pursuant to 37 CFR 41.39(b)(2) is accompanied by any amendment, affidavit or other evidence, it shall be treated as a request that prosecution be reopened before the primary examiner under 37 CFR 41.39(b)(1).

Extensions of time under 37 CFR 1.136(a) are not applicable to the TWO MONTH time period set forth above. See 37 CFR 1.136(b) for extensions of time to reply for patent applications and 37 CFR 1.550(c) for extensions of time to reply for ex parte reexamination proceedings.

Respectfully submitted,

/GiGi Huang/

Examiner, Art Unit 1612

Conferees

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614

A Technology Center Director or designee must personally approve the new ground(s) of rejection set forth in section (9) above by signing below:

/Andrew Wang/

Acting Director of Technology Center 1600